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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/077,574	09/24/1998	MICHAEL PANACCIO	DAVIE60001AP	6196

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	22

DATE MAILED: 05/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/077,574	Panaccio et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 5, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-62 and 92-115* ~~is~~/are pending in the application.

4a) Of the above, claim(s) *3-5, 11, 13-31, 33-36, 42, 44-62, 92, 93, 96-107* and 110-113 ~~is~~/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 6-10, 12, 32, 37-41, 43, 94, 95, 108, 109, 114, and 115* ~~is~~/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *18.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 03/05/02 (paper no. 20) in response to the non-final Office Action mailed 08/29/01 (paper no. 16). With these, Applicants have amended the specification.

Status of Claims

2) Claims 1, 6-10, 32, 37-41, 94, 95 and 109 have been amended via the amendment filed 03/05/02.

New claims 114 and 115 have been added via the amendment filed 03/05/02.

Claims 1-62 and 92-115 are pending.

Claims 1, 2, 6-10, 12, 32, 37-41, 43, 94, 95, 108, 109, 114 and 115, to the extent these claims encompass the polypeptide of SEQ ID NO: 2, are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' Information Disclosure Statement filed 03/05/02 (paper no. 18). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 22).

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 8 of the Office Action mailed 08/29/01 (paper no. 16) is withdrawn in light of Applicants' amendments to the specification.

7) The objection to claim 95 made in paragraph 19(b) of the Office Action mailed 08/29/01

(paper no. 16) is withdrawn in light of Applicants' amendment to the claim.

Objection(s) Maintained

8) The objection to claims 12 and 94 made in paragraph 19(b) of the Office Action mailed 08/29/01 (paper no. 16) is maintained for reasons set forth therein.

9) The objection to claim 108 made in paragraph 19(c) of the Office Action mailed 08/29/01 (paper no. 16) is maintained for reasons set forth therein.

Rejection(s) Withdrawn

10) The rejection of claims 41 and 43 made in paragraph 9 of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, first paragraph, as being non-enabled, is withdrawn.

11) The rejection of claims 6, 32, 37, 38 and 41 made in paragraph 12(a) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim(s) and/or the base claim(s).

12) The rejection of claim 40 made in paragraph 12(b) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

13) The rejection of claim 41 made in paragraph 12(c) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn.

14) The rejection of claims 9 and 40 made in paragraph 12(d) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

15) The rejection of claims 9 and 40 made in paragraph 12(e) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

16) The rejection of claims 37, 38 and 39 made in paragraph 12(f) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

17) The rejection of claims 10 and 94 made in paragraph 12(g) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

18) The rejection of claim 109 made in paragraph 12(h) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

19) The rejection of claims 94 and 95 made in paragraph 12(i) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

20) The rejection of claim 95 made in paragraph 12(j) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

21) The rejection of claims 2, 12, 43, 108 and 109 made in paragraph 12(k) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

22) The rejection of claims 1, 2 and 6-9 made in paragraph 15 of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C. § 102(b) as being anticipated by Labigne *et al.* (WO 94/26901 - Applicants' IDS), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

23) The rejection of claims 32, 37-41 and 43 made in paragraph 17 of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C. § 103(a) as being unpatentable over Labigne *et al.* (WO 94/26901 - Applicants' IDS), is withdrawn in light of Applicants' amendments to the claims and/or the base claim(s).

Rejection(s) Maintained

24) The rejection of claims 38-43 made in paragraph 10 of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, first paragraph, as being non-enabled, is maintained for reasons set forth therein and hereblow.

Applicants contend that the amended claims recite that the derivative must be "immunogenically reactive". Applicants state that one of skill in the art would be able to identify an "immunologically reactive" derivative by identifying the antigenic region experimentally or using a computer program [Emphasis added].

Applicants' arguments have been carefully considered, but are non-persuasive. Contrary to the Applicants' statement, claim 38 has been amended to include the limitation: "wherein said derivative is still immunogenic". The instant specification, however, does not teach how to produce such a derivative which remains immunogenic and induces a protective immune response against *L. intracellularis*, or an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*. As explained in detail in paragraph 10 of the Office Action mailed 08/29/01 (paper no. 16), there is neither evidence within the instant specification, nor is there any certainty that an immunogenic derivative of a peptide or a protein, would retain the capacity to induce an immune response that is broadly protective against *L. intracellularis*, or an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*, as claimed. A derivative of a peptide or a protein that induces an immune response that is broadly 'protective' against *L. intracellularis*, or an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia* cannot be predicted by using a computer program. Given the lack of guidance in the specification and the art-recognized unpredictability in determining amino acid variations that are acceptable, one of ordinary skill in the art could not make or use the claimed immunogenic and 'protective' 'derivative', without undue experimentation.

25) The rejection of claims 6 and 7 made in paragraph 12(a) and the rejection of claims 8 and 9 made in paragraph 12(k) of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C § 112, second paragraph, as being indefinite, are maintained for reasons set forth therein.

Applicants state that they have amended claim 6 specifying that the related microorganism is an isolate or subspecies of *L. intracellularis* or other species of the *Lawsonia*. However, no such amendments have been made to claim 6.

26) The rejection of claims 1, 2, 6, 7, 32, 37 and 38 made in paragraph 14 of the Office

Action mailed 08/29/01 (paper no. 16) under 35 U.S.C. § 102(e) as being anticipated by Knittel *et al.* (US 5,714,375) as evidenced by Lemarchand *et al.* (*Vet. Pathol.* 34: 152-156, March 1997, abstract), is maintained for reasons set forth therein and herebelow.

Applicants contend that the "antigen" taught by Knittel *et al.* is the whole attenuated bacteria and that Knittel *et al.* does not teach or suggest an immunogenic component or subunit-type vaccine.

The Applicants' argument has been carefully considered, but is non-persuasive. It should be noted that the instant base claim includes the transitional term "comprising", which is synonymous with "including," containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (*Fed. Cir.* 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (*CCPA* 1981); *Ex parte Davis*, 80 USPQ 448, 450 (*Bd. App.* 1948) ("comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts"). It should also be noted that the limitation "immunogenic component" is described in the specification as encompassing *Lawsonia intracellularis* in attenuated, non-pathogenic or killed form (see page 4, lines 15 and 16). Knittel's whole attenuated bacterial antigen thus qualifies as an 'immunogenic component' of *Lawsonia intracellularis,* or inherently "comprises" an "immunogenic component" or the peptide or protein of *L. intracellularis* as recited in claims 6 and 37. It is important to note that instant claims are not limited to an isolated and/or purified immunogenic component of *L. intracellularis*, but broadly encompass a non-isolated and/or non-purified *L. intracellularis* immunogenic component. Furthermore, Example 5 of Knittel *et al.* also describes a partially purified antigen of *L. intracellularis* that has been passed through a 22 gauge needle and centrifuged to remove cellular nuclei and debris.

27) The rejection of claims 1, 2, 6-8, 32 and 37-39 made in paragraph 18 of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C. § 103(a) as being unpatentable over Joens *et al.* (US 5,610,059), is maintained for reasons set forth therein.

Applicants contend that *prima facie* obviousness requires a recitation of all of the claimed

elements. Applicants state that Joens *et al.* do not teach all of the claim elements, the specific microorganism and a method of vaccinating with *L. intracellularis*. Applicants assert that Joens *et al.* do not teach any proteins that are specifically immunogenic and a method of vaccinating with recombinant or subunit from *L. intracellularis*.

Applicants' arguments have been carefully considered, but are non-persuasive. As set forth in paragraph 18 of the Office Action mailed 08/29/01 (paper no. 16), Joens *et al.* was applied as prior art under 35 U.S.C. § 103 as opposed to 35 U.S.C. § 102. Instant claims are not limited to the use of a recombinant or subunit vaccine from *L. intracellularis*. Joens *et al.* clearly taught a purified PPE-causing agent and how one of skill in the art can produce a bacterin, a subunit preparation, fusion proteins, purified cell-surface proteins and recombinant antigens that are useful as vaccines for prophylactic treatments. Contrary to the Applicants' statement that Joens *et al.* do not teach the specific microorganism, the instant specification itself describes PPE-causing agent to be the same as *L. intracellularis* (see paragraph bridging pages 1 and 2 and page 2). Furthermore, it should be noted that instant claims (method claims) are not limited to a method of vaccinating an animal using a recombinant or a subunit antigen from *L. intracellularis*, but broadly encompasses a method of vaccination with a vaccine "comprising" a non-isolated and non-purified immunogenic component of *L. intracellularis*. It is understood to those skilled in the art that a purified PPE-causing agent "comprises" an immunogenic component. The rejection stands.

28) The rejection of claim 94 made in paragraph 15 of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C. § 102(b) as being anticipated by Labigne *et al.* (WO 94/26901 - Applicants' IDS), is maintained for reasons set forth therein and herebelow.

Applicants state that Labigne's recombinant immunogenic composition of *H. felis* or *H. pylori* may be related to *L. intracellularis*, but is not to the same genus. Applicants assert that Labigne does not anticipate claim 94, because the claim is amended to recite "wherein said related microorganism is an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*".

Applicants' arguments have been carefully considered, but are non-persuasive. Contrary to the Applicants' assertion, claim 94 is not amended to include the recitation: "wherein said related microorganism is an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*". The claim does not make a mention of any *Lawsonia*. The rejection stands.

29) The rejection of claims 94 and 95 made in paragraph 17 of the Office Action mailed 08/29/01 (paper no. 16) under 35 U.S.C. § 103(a) as being unpatentable over Labigne *et al.* (WO 94/26901 - Applicants' IDS), is maintained for reasons set forth therein and herebelow.

Applicants contend that the claim is amended to specify that the related microorganism "is an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*". Applicants state that Labigne does not render the method obvious, because Labigne teaches a method for vaccination against a completely different microorganism which is not a species of the genus *Lawsonia*, but of the genus *Helicobacter*.

Applicants' arguments have been carefully considered, but are non-persuasive. Contrary to the Applicants' assertion, claim 95 is not amended to include the recitation: "wherein said related microorganism is an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*". The claims do not make a mention of any *Lawsonia*. The rejection stands.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office. The new rejection is necessitated by Applicants' amendments to the base claim(s) and/or addition of new claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph

30) Claims 9 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9, 38 and 40, as amended, include the limitation "wherein said derivative is still immunogenic". However, there appears to be no support in the instant specification for such a

limitation. Therefore, the above-identified limitation(s) in the claim(s) is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation, or to remove the new matter from the claim(s).

31) Claims 1, 32 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 32 and 41, as amended, include the recitation "wherein said related microorganism is .... **subspecies** of *L. intracellularis*" [Emphasis added]. However, there appears to be no support in the instant specification for such a limitation. Therefore, the above-identified limitation(s) in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation, or to remove the new matter from the claim(s).

32) Claims 1, 2, 6-9, 10, 12, 32, 37-41, 43, 94, 95, 108, 109, 114 and 115 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a whole formalin-killed *L. intracellularis* vaccine that decreases the shedding of *L. intracellularis* in pigs and a method of decreasing the shedding of *L. intracellularis* in pigs by administering the same, and for a composition comprising an isolated polypeptide of the amino acid sequence of SEQ ID

NO: 2 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a 'vaccine' composition comprising any isolated immunogenic component, including the polypeptide of SEQ ID NO: 2 alone or in combination with other *Lawsonia intracellularis* antigens or immunogenic components, wherein the components elicit a homologous or heterologous protective immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims are drawn to a vaccine composition comprising an immunogenic component of *L. intracellularis* or a related microorganism which is an isolate or a "subspecies of *L. intracellularis*" or an immunogenic component of "other species of the genus *Lawsonia*", including a peptide or a protein and a method of vaccination using the same. The limitation "immunogenic component" is described in the specification as encompassing *Lawsonia intracellularis* in attenuated, non-pathogenic or killed form (see page 4, lines 15 and 16). As claimed currently, the immunogenic component, the peptide or the protein encompasses an isolated and a non-isolated immunogenic component, the peptide or the protein. However, with regard to the vaccine composition, the enbling disclosure in the instant specification is limited to a showing that a whole formalin killed *L. intracellularis* serves to reduce the shedding of *L. intracellularis* bacteria. Example 15 shows that pigs vaccinated with a whole formalin killed *L. intracellularis* vaccine as set out in Example 12 shed decreased number of *L. intracellularis* bacteria. The description in Example 20 is limited to the statement that DNA molecules

encoding "putative vaccine candidates" were identified using BLAST and amino acid sequences having sequence 'similarity' to certain proteins. SEQ ID NO: 2 in the instant specification is described as a GroEL protein (see page 6, lines 23 and 24; and Example 9). However, there is no enabling disclosre that the polypeptide of SEQ ID NO: 2, refolding heat-shock protein, or any other isolated immunogenic component of *L. intracellularis* or a related microorganism that happens to be an isolate or a subspecies of *L. intracellularis* induces a 'protective' immune response. A "vaccine", even when defined in a broad sense, is required to stimulate a 'protective immune response'. See Klesius *et al.* (US 6,379,677, lines 26-29 in column 2). A mere sequence comparison is insufficient to predict the protective capacity of a microbial antigen. Clearly, the protective capacity of an isolated immunogenic component, a peptide or a protein of an isolate of *Lawsonia intracellularis*, let alone that of a subspecies of *Lawsonia intracellularis*, or other species of the genus *Lawsonia*, or a polypeptide that is immunologically similar to the polypeptide of SEQ ID NO: 2, has not been enabled or established. The specification fails to teach that the antibody response to the polypeptide of SEQ ID NO: 2, or a polypeptide that is immunologically cross-reactive with the antibodies to the polypeptide of SEQ ID NO: 2 would serve as a vaccine composition, i.e., has the capacity to confer a protective immune response against infection by an isolate of *Lawsonia intracellularis*, or a related microorganism which is a subspecies of *Lawsonia intracellularis*, or other species of the genus *Lawsonia*, as claimed currently. Vaccines are required to elicit an immunoprotective response in the vaccinated host, as opposed to having a mere capacity to serve as antigens with specific binding abilities, or as immunogens with an ability to elicit an antibody or immune response. The art of vaccines recognizes the unpredictability associated with whether an antigen or immunogenic component derived from a microbial pathogen is immunoprotective. For instance, Ellis RW (*Vaccines*, (Eds) Plotkin *et al.*, W.B. Saunders Company, Philadelphia, Chapter 29, 1988, see page 571, second full paragraph) reflects this problem in the teaching that the key to the problem of vaccine development "is the identification of that protein component of a ..... microbial pathogen that itself can elicit the production of protective antibodies ..... and thus protect the host against

attack by the pathogen". In the instant case, the specification fails to teach or show that the isolated polypeptide of the amino acid sequence SEQ ID NO: 2, alone or in combination with other antigens, does in fact induce an immune response that is protective against the homologous *Lawsonia intracellularis* isolate, or subspecies of *Lawsonia intracellularis*, or against any other heterologous species of the genus *Lawsonia*. The selection of an immunogenic component that is protective from a myriad of immunogenic components present on the microbial surface, or produced by a microbial pathogen cannot be accomplished with a predictable precision, without undue experimentation. Furthermore, the specification does not teach any 'immunogenic component', proteinaceous or non-proteinaceous, from a "related microorganism" which is a "subspecies of *Lawsonia intracellularis* or other species of the genus *Lawsonia*". The only *Lawsonia* species identified in the instant specification is *Lawsonia intracellularis* (see page 2 and paragraph bridging pages 3 and 4). No "subspecies" of *Lawsonia intracellularis,* or 'other species' of the genus *Lawsonia* are mentioned or identified in the instant specification, let alone an 'immunogenic component' from such species or subspecies, that does or does not have the ability to induce a protective immune response "against *Lawsonia intracellularis* or related microorganism, wherein said related microorganism is an isolate or subspecies of *Lawsonia intracellularis* or other species of the genus *Lawsonia*". There is absolutely no evidence or guarantee that an isolated immunogenic component of an isolate of *Lawsonia intracellularis* would be therapeutic or protective against an isolate of *Lawsonia intracellularis*, or subspecies of *Lawsonia intracellularis* or other species of the genus *Lawsonia*. The specification fails to teach that the mere presence of antibodies which bind to the polypeptide of SEQ ID NO: 2 provides protection from infection by an isolate of *Lawsonia intracellularis*, or subspecies of *Lawsonia intracellularis* or other species of the genus *Lawsonia*. There is no evidence within the instant specification that the claimed polypeptide, or a polypeptide that has immunological similarity to the claimed polypeptide, is able to perform as a vaccine by conferring protection, or eliminating the disease, or lowering the morbidity and/or mortality of the disease caused by an isolate of *Lawsonia intracellularis*, or subspecies of *Lawsonia intracellularis* or other species of the genus

Lawsonia.

Absent a showing that an isolated immunogenic component, or the polypeptide or peptide of SEQ ID NO: 2, is effective in inducing a 'protective' immune response against homologus infection by an isolate of *Lawsonia intracellularis*, or against a heterologous infection by a subspecies of *Lawsonia intracellularis*, or any other species of the genus *Lawsonia*, a vaccine composition and a method of vaccination as claimed are not enabled. In view of the lack of teachings within the instant specification, the breadth of the claims, the unpredictability recognized in the art, and the quantity of the experimentation required, undue experimentation would have been required by one of ordinary skill in the art to reproducibly practice the full scope of the invention, as claimed.

33) Claims 41, 43 and 109 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims are drawn to a method of vaccination using a polypeptide comprising an amino acid sequence that is at least "40% similar" to SEQ ID No. 2. However, the instant specification does not provide enablement for such a polypeptide that is 40% similar to SEQ ID NO: 2 and that induces a "protective" immune response against an isolate of *Lawsonia intracellularis*, or subspecies of *Lawsonia intracellularis* or other species of the genus *Lawsonia*. The specification fails to teach the precise structural composition of the claimed polypeptide. It

is not clear to one of ordinary skill in the art whether 40% similarity represents continuous or discontinuous similarity to SEQ ID NO: 2. It is uncertain whether retaining 40% continuous or discontinuous similarity from any part of SEQ ID NO: 2 (i.e., terminal or central parts) would yield a polypeptide that has the ability to induce a protective immune response against "an isolate of *Lawsonia intracellularis*, or subspecies of *Lawsonia intracellularis* or other species of the genus *Lawsonia*". There is lack of disclosure as to 40% homologous amino acid residues from which region of SEQ ID NO: 2 are encompassed in the claimed polypeptide which is required to induce a protective immune response not only against an isolate of *Lawsonia intracellularis*, but also against a subspecies of *Lawsonia intracellularis* or other species of the genus *Lawsonia*. It is unlikely that a polypeptide having 40% continuous or discontinuous similarity to any part of SEQ ID NO: 2 would retain the desired/recited immunological specificity of the polypeptide of SEQ ID NO: 2 in such a way that it elicits a homologous or heterologous protective immune response. Without a disclosure of the specific amino acid residues contained within the claimed polypeptide, one of ordinary skill in the art cannot be sure of the sequence embraced by the claims and would not be able to make and use the polypeptide sequence as recited in the instant claims, without undue experimentation. One of ordinary skill in the art would not be able to make and use such a polypeptide sequence, for example, as a prophylactic, or therapeutic reagent, because there is no disclosure as to what amino acid residues are embraced by the claimed polypeptide and whether these sequences possess the ability to induce a protective immune response. This is critical in view of the following. It is clear that, although the claimed polypeptide is said to have 40% similarity with SEQ ID NO: 2, there is a 60% dissimilarity between SEQ ID NO: 2 and the claimed polypeptide, and the effects of this dissimilarity upon protein structure and function cannot be predicted. Bowie *et al* (*Science*, 1990, 247: 1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into a unique three-dimensional structure that allows it to function and carry out the instructions of the genome. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted

structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). Bowie *et al* also teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence is exemplified by Burgess *et al.* (*J. Cell Biol.* 111: 2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similar teachings are provided by Lazar *et al.* (*Mol. Cellular Biol.* 1988, 8: 1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. All these references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein or a polypeptide. Thus, when the art has establishes that a single amino acid dissimilarity can drastically change the functions of a given polypeptide or a protein, clearly, the functional integrity of the claimed polypeptide having 60% dissimilarity to the polypeptide of SEQ ID NO: 2 could not be predicted, solely based on the sequence similarity, nor would it be expected to be the same as that of the polypeptide of SEQ ID NO: 2.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

34) Claims 1, 2, 6-9, 32, 37-41, 43, 94, 95, 109, 114 and 115 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1, 32 and 41 are vague and indefinite in the recitation: "subspecies of *L. intracellularis* or other species of the genus *Lawsonia*", because it is unclear what is

encompassed in the recitation "subspecies" and "other species". It is unclear how an 'isolate' of *L. intracellularis* differs from a "subspecies" of *L. intracellularis*. It is not clear what characteristics a related microorganism should have in order to qualify as a "subspecies" of *L. intracellularis*. It is not clear what the limitation "other species of the genus *Lawsonia*" represent.

(b) Claim 6 does not further limit claim 1 with regard to the recitation "related microorganism". Claim 6 depends from claim 1 which recites a "related microorganism" that is limited o "an isolate or subspecies of *L. intracellularis* or other species of the genus *Lawsonia*". However, the limitation "related microorganism" in claim 6 broadens the scope.

(c) Claim 114 is vague and indefinite in the recitation "immunogenic component is ..... SEQ ID NOS:...", because it is unclear whether these SEQ ID numbers represent a polynucleotide or a polypeptide.

(d) Claim 95 is vague and confusing in the recitation "immunologically" effective amount of a polypeptide (see line 3). The claim is drawn to a method of vaccination by using a polypeptide meant to be immunogenic. It is unclear what Applicants mean by an "immunologically" effective amount of a polypeptide. Is it equivalent to "immunogenically" effective amount?

(e) Claims 94 and 95 are vague, indefinite and confusing in the recitation "a polypeptide that is immunologically cross reactive with a polypeptide", because it is unclear how a polypeptide can be immunologically cross reactive with another polypeptide. The cross reactivity of one polypeptide is usually seen with antibodies specific to another polypeptide, but not with another polypeptide itself. Clarification/correction is requested.

(f) Claim 43 is confusing and/or lacks antecedent basis for the recitation: "the immunogenic component comprises .... polypeptide". Claim 43 depends from claim 38, which recites "said" immunogenic component that comprises "a peptide, protein", but not a polypeptide. Clarification/correction is requested.

(g) Claims 9 and 40 are confusing in the recitation "a refolding and heat shock

protein". It is unclear whether this is a single protein? If Applicants intend to convey that refolding is a property of the recited heat shock protein, it is suggested that Applicants replace the recitation with --a refolding heat shock protein--.

(h) Claim 95 is vague and indefinite in the recitation: "related microorganism", because it is unclear what is encompassed in this phrase. It is not clear what characteristics or properties a microorganism should have in order to qualify as a 'related microorganism'.

(i) Claims 1, 32 and 41 are confusing in the recitation "an immunogenic component **of *L. intracellularis*** or related microorganism, wherein said related microorganism is **an isolate ..... of .... *L. intracellularis***" [Emphasis added]. It is unclear what the differences are, if any, between *"L. intracellularis"* and a related microorganism that is "an isolate of *L. intracellularis*". Furthermore, it is unclear what Applicants mean by "subspecies of *L. intracellularis*", or what characteristics an *L. intracellularis* should have in order to qualify as a "subspecies" of *L. intracellularis*.

(j) Claims 2, 6-9, 37-40, 43, 109, 114 and 115, which depend from one of the base claims identified above, are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite, because of the vagueness or indefiniteness, identified above in the base claim(s).

Objection(s)

35) Instant claims are objected to for the following reasons:

(a) Claims 114 and 115 are objected to for including non-elected subject matter.

(b) Claims 1, 6, 7, 32, 41 and 95 are objected to for lacking a preceding article before the recitation "related microorganism". It is suggested that Applicants replace the recitation with --a related microorganism--.

Relevant Prior Art

36) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- McOrist *et al.* (*Inter. J. Systematic Bacteriol.* 45: 820-825, October 1995) teach purified DNAs and recombinant DNA probes unique to *IS intracellularis* strains (see abstract;

and page 821).

Remarks

37) Claims 1, 2, 6-10, 12, 32, 37-41, 43, 94, 95, 108, 109, 114 and 115 stand rejected.

38) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

39) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD

S. DEVI, PH.D.
PRIMARY EXAMINER

May, 2002